

EXHIBIT 6

Consensus guidelines: Preconception counseling, management, and care of the pregnant woman with epilepsy*

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Article abstract—All women with epilepsy who are of childbearing age should be advised (preferably before conception) that the incidence of malformations in infants of mothers with epilepsy who are treated with antiepileptic drugs (AEDs) is two or three times that of infants of mothers without epilepsy. In addition, children of mothers with epilepsy, treated or untreated with AEDs, tend to have slightly more minor anomalies than do children of fathers with epilepsy or control subjects. We do not know which of the four major AEDs (phenytoin, carbamazepine, valproate, and phenobarbital) is the most teratogenic. If AED treatment cannot be avoided, the first-choice drug for the seizure type and epilepsy syndrome should be used as monotherapy at the lowest effective dose. Diet prior to conception and during organogenesis should contain adequate amounts of folate. Prenatal diagnosis of possible birth defects should be offered, and patients should be followed closely during pregnancy, labor, and puerperium. Despite the small but significant risks, more than 90% of women with epilepsy who receive AEDs during pregnancy will deliver normal children free of birth defects.

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On July 13 and 14, 1990, clinician-investigators gathered for a workshop-symposium to discuss the pressing and primary issues surrounding the use of antiepileptic drugs (AEDs) during pregnancy. During the workshop-symposium, principal investigators from Rotterdam, The Netherlands; Helsinki; Berlin; Hirosaki, Japan; Montreal; Marseilles, France; San Diego; and Portland, Oregon, updated the results of their prospective cohort studies of pregnant women with epilepsy. During subsequent open discussions, leading epileptologists questioned investigators about their projects, and together these experts reviewed the firmly established data, the assumptions they could make, and the logic they could use to reach conclusions and recommend clinically prudent guidelines.

From the practitioner's point of view, the primary question is whether the evidence and analyses presented during the workshop-symposium by various investigators, most of which are included in this supplement, reasonably support a conclusion

that the four frontline AEDs—phenytoin, carbamazepine, valproate, and phenobarbital—are safe and effective treatment for pregnant women with epilepsy. Beyond a simple yes or no answer to the question, the practitioner seeks to hear the basis for such an answer and requests guidelines that can optimize care for the pregnant woman with epilepsy.

The guidelines presented here are intended to aid the practitioner in making decisions in counseling women before pregnancy and in treating seizures during pregnancy. They enumerate the principles of management and specific practical recommendations, based on the proceedings and deliberations of the 1990 workshop-symposium. In so doing, the guidelines should clarify areas that have recently achieved a substantial degree of authoritative acceptance and, hence, consensus. The guidelines also should point out unanswered questions and concerns still in dispute. As a start, practitioners should follow the Guidelines for the

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Table 1. Guidelines: counseling women who plan pregnancy*

1. The risk of major malformations, minor anomalies, and dysmorphic features is twofold to threefold higher in infants of mothers with epilepsy who receive treatment with antiepileptic drugs (AEDs) compared with the risk in infants of mothers without epilepsy.
2. A possibility exists that some of the risk is caused by a genetic predisposition for birth defects inherent in certain families. Both parents' family histories should be reviewed for birth defects.
3. Possibilities for prenatal diagnosis of major malformations should be discussed. If valproate or carbamazepine is the necessary AED, the likelihood of amniocentesis and ultrasound examinations during pregnancy should be discussed. Ultrasound examination for a variety of major malformations can be done during the 18th to 22nd weeks.
4. Effects of tonic-clonic seizures on the fetus during pregnancy are not well established. However, tonic-clonic convulsions might be deleterious to the fetus, injure the mother, and lead to miscarriage.
5. The diet prior to conception should contain adequate amounts of folate.
6. If the patient is seizure free for at least 2 years, eg, free from absences, complex partial, or tonic-clonic attacks, withdrawal of AED should be considered.
7. If AED treatment is necessary, a switch to monotherapy should be made if possible.
8. The lowest AED dose and plasma level that protects against tonic-clonic, myoclonic, absence, or complex partial seizures should be made if possible. Closed-circuit television electroencephalographic monitoring should be used if necessary.

* All women of childbearing age should be informed of these guidelines.

Care of Epileptic Women of Childbearing Age, developed by the Commission on Genetics, Pregnancy, and the Child for the International League Against Epilepsy (ILAE).¹

Counseling women who plan pregnancies.

Counseling should start reassuring the patient that most women with epilepsy can achieve a very good obstetric and neonatal outcome, provided adequate care is available² (table 1). Good nutrition and health before conception, careful prenatal care, adequate sleep, maintenance of adequate or normal serum folate levels during the first months of pregnancy, and good seizure control with the lowest plasma level of AED that protects against tonic-clonic convulsions can reduce the likelihood of adverse pregnancy outcomes. In the majority of women with epilepsy, the frequency of seizures does not increase during pregnancy³⁻⁷; 17 to 37% will show an increase, but many of these women are sleep deprived or deliberately noncompliant because of their concerns about the effects of AEDs on their offspring.^{3,4,6,7}

Except in rare patients (1 to 2%) who have a convulsion, labor and delivery proceed without increased complications. Nevertheless, slightly more inductions of labor, mechanical ruptures of membranes, forcep-assisted deliveries, and cesarean sections appear to be performed in women with epilepsy.^{6,8,9} However, in a population-based study in Finland, such procedures were performed equally often in 160 pregnancies of women with epilepsy, as compared with 160 control pregnancies.^{10,11} Hence, Hilesmaa² contends that these procedures are unjustified in most instances.

A slight increase in the common complications of pregnancy, such as toxemia, preeclampsia, bleeding, placental abruption, and premature labor, has been reported for women with epilepsy.³⁻⁸ The relative risk for these complications is calculated to be

1.5 to 3 times that of women without epilepsy, but no agreement on this matter has been reached.^{8,10-12} Most reports have been retrospective^{4,5,8,9,12} or registry-based,^{4,5} and some obstetric series show only minimal or no increased risk.^{6,10,11,13}

The keys to good outcome include good nutrition and health before conception, good prenatal care, and regular neurologic follow-up for seizure control. Patients must be counseled against the use of cigarettes, recreational drugs and alcohol, and other medications, except as directed by a physician. The consensus today is that more than 90% of women with epilepsy who receive AEDs will deliver normal children, free of birth defects, and that prospective and retrospective studies^{6,14-27} have identified unequivocal risks for major malformations and minor anomalies in a small but significant percentage of fetuses (6 to 8%) exposed in utero to AEDs (phenytoin, carbamazepine, valproate, phenobarbital).

Risks to the fetus are probably higher when AEDs are used in combination and when there is a family history of birth defects.²⁸ All women with epilepsy who are of childbearing age should, therefore, be advised (preferably before conception) that the incidence of malformations in infants of mothers with epilepsy who are treated with AEDs is two or three times that of infants of mothers without epilepsy. Children of mothers with epilepsy, treated or untreated with AEDs, tend to have slightly more minor anomalies than do children of fathers with epilepsy or control subjects.²⁴

Which of the frontline AEDs is more teratogenic? Congenital major malformations. Major malformations are structural defects formed during the development of an organ or organ system that could result in significant dysfunction or death. Surgical intervention is usually necessary to alleviate or correct the condition. Examples of major

malformations are neural-tube defects, congenital heart disease, orofacial clefts, intestinal atresia, and deformities of kidney or ureters.

To date, no information is available as to which of the four major AEDs (phenytoin, carbamazepine, valproate, and phenobarbital) is the most teratogenic and causes more major malformations. Koch et al²⁴ present suggestive, but inconclusive, evidence that valproate, when used as monotherapy during pregnancy, is "considerably teratogenic," whereas phenytoin and phenobarbital are "weakly teratogenic." In this 1991 German collaborative study²⁴ and in separate reports by DiLiberti et al,²⁵ Jäger-Roman et al,²⁶ Robert and Guibaud,²⁷ and Lindhout et al,²⁹⁻³² valproate is claimed to produce a different and almost specific pattern of major malformations—consisting of meningocele and cardiovascular and urogenital malformations—with craniofacial, skeletal, and genital minor anomalies. One to two percent of fetuses exposed in utero to valproate are likely to develop neural-tube defects^{31,32} and the association is likely to be with spina bifida aperta and not with anencephaly.³² Most often, an open lumbosacral myelocele is observed.³²

Because of the above reports on valproate and earlier reports of cleft lip-palate and congenital heart and urogenital defects associated with phenytoin,^{17,19,21} many practicing neurologists have favored the use of carbamazepine during pregnancy. Unfortunately, carbamazepine also has been associated with major malformations, as was suggested first by Lindhout et al,²⁹ and most recently by Rosa.³³

Lindhout et al noted the association of major malformations²⁹ and spina bifida³⁰⁻³² with the use of carbamazepine alone or in combination with valproate. Rosa calculated that approximately 0.9% of fetuses exposed in utero to carbamazepine have spina bifida aperta.³³

Although Koch et al²⁴ consider phenytoin and phenobarbital "weakly teratogenic," both drugs have been associated with serious malformations of the heart, orofacial, and urogenital structures in infants.^{31,34} Unfortunately, the number of cohorts exposed to these drugs as monotherapy has not been large enough to permit a determination about whether either drug is associated with these major defects and, if so, what their true prevalence is.

In the Montreal series,^{14,35} ventricular septal defect and cleft lip and palate were the most frequent malformations. They were associated with high plasma levels of phenytoin and phenobarbital.³⁵ The updated report of this Montreal study³⁶ showed that in monotherapy, the highest frequency of developmental defects was observed with valproate, followed by phenytoin and carbamazepine. Analyzed as a single drug or as a drug in combination, primidone was associated with the highest frequency of malformations, whereas carbamazepine was associated with the lowest. Phenobarbital, phenytoin, and valproic acid were

associated with intermediate frequencies. Kaneko et al³⁴ observed heart defects associated with methylphenobarbital. Both Kaneko et al³⁴ and Lindhout et al³¹ also noted heart defects in valproate-exposed infants, but the latter observed such malformations only after valproate polytherapy.

In the French prospective cohort study,³⁷ eight cases of congenital heart disease were observed in infants of 146 women exposed to phenobarbital, and none were seen in infants of 69 women not exposed to phenobarbital. Three of the mothers of children with heart defects received both phenytoin and phenobarbital. These researchers considered valproate and phenytoin to be the most teratogenic drugs in their population sample, because phenytoin in polytherapy was significantly associated with malformations, such as heart defects, and because two infants with spina bifida were born to valproate-exposed mothers.

The foregoing information demonstrates that each of the four major AEDs has been considered more teratogenic than the other three AEDs, depending on the author cited, but that results are confounded by the use of polypharmacy, different dosages and combinations of AEDs, different patient populations, and different genotypes exposed to the AEDs. To complicate the issue further, a few controlled studies have shown the absence of congenital heart defects or no association of such defects with AED exposure in utero.^{6,11,38,39} All these conflicting results can produce confusion in the mind of the practitioner about which agent to prescribe during pregnancy. Since no agreement has been reached regarding which AED is the most teratogenic, the present consensus opinion is that the AED that stops seizures in a given patient should be used. Often, this is the drug of choice for a given seizure type and epilepsy syndrome.

All now agree that, if possible, only one AED should be used during pregnancy and that it should not be used in combination with any other drug (polytherapy). Besides genetic background, polytherapy is a primary factor associated with a higher incidence of heart defects, cleft lip/palate, and dysmorphism with retardation noted in offspring of mothers with epilepsy.^{24,40-42} In particular, valproate plus carbamazepine plus phenobarbital, with or without phenytoin, was associated with malformations in 7 of 12 exposed infants.²⁹

In recent, independent studies from The Netherlands,³¹ Japan,³⁴ and Canada³⁵ (see articles in this supplement), the reduction and near-elimination of polypharmacy—especially the valproate, carbamazepine, and phenobarbital triad—and the institution of monotherapy significantly reduced the overall prevalence of malformations, from 13.5 to 6.2%³⁴ or from 9.9 to 7.6%.³¹ The pattern of malformations also appears to have changed from that of congenital heart defects, facial clefts, and syndromes of dysmorphism with developmental retardation associated with polypharmacy, to that of

Table 2. Relative timing and developmental pathology of certain malformations

Tissues	Malformations	Approximate interval after first day of last menstrual period
Central nervous system	Meningomyelocele	28 days
Face	Cleft lip	36 days
	Cleft maxillary palate	10 weeks
Heart	Ventricular septal defect	6 weeks

spinal defects and glandular hypospadias^{24,31} associated with monotherapy. Women with epilepsy who are planning pregnancy should therefore be informed of the small, but real, risk for major malformations associated with AEDs and of the period of gestation during which these malformations are apt to occur (table 2).

Because in utero exposure to trimethadione has been associated with a high prevalence of severe birth defects, physical anomalies, growth retardation, and mental retardation, many consider trimethadione to be absolutely contraindicated during pregnancy.^{15,43-45}

In conclusion, none of the available reports to date have studied a sufficiently large number of women with epilepsy exposed to AED monotherapy during pregnancy. Consequently, inadequate power has skewed the statistical analysis of risk estimates for specific forms of major birth defects associated with specific AEDs. The denominator used for analysis of each AED combination in polytherapy is even smaller.

Congenital minor malformations and dysmorphic anomalies. Minor malformations and dysmorphic anomalies are commonly found together. Minor congenital malformations are structural defects found during development of an organ or limb that impede or impair function but do not result in serious illness or death if not medically treated or surgically modified. Examples are club foot, equinovarus, and hypospadias. Minor dysmorphic anomalies are unusual morphologic features of no serious medical consequence to the patient. These are appearances or structural changes in the superficial aspects of the face or limbs that have no primary impact on function. Examples are hypertelorism; epicanthal folds; broad, flat nasal bridge; upturned nasal tip; long philtrum; wide mouth; rotated ears; prominent occiput; and distal digital hypoplasia.

Prospective mothers come to the clinics already informed by the lay press, expressing fear for the panoply of dysmorphic features, multiple minor physical anomalies, and skeletal defects so often ascribed to the "antiepileptic drug fetal syndrome."⁴⁶ In the past, these dysmorphic features

incorrectly were blamed solely and specifically on phenytoin.^{47,48}

In 1975, Hanson and Smith observed such phenomena in infants exposed in utero to phenytoin and dubbed their findings "fetal hydantoin syndrome."⁴⁸ In the same year, a similar combination of anomalies was associated with trimethadione and was called "fetal trimethadione syndrome."⁴⁵ Soon after, a "primidone embryopathy"⁴⁹ was reported. Finally, Jones et al⁵⁰ reported a pattern of malformation with minor craniofacial defects, fingernail hypoplasia, and developmental delay similar to that observed after in utero exposure to phenytoin: a "pattern of malformations seen with prenatal carbamazepine exposure."⁵⁰

Many authors have since argued that it would make more sense to place all these anomalies under the rubric of "fetal antiepileptic drug syndrome."^{38,46} Convincing evidence that all components of minor malformations and dysmorphism are derived from intrauterine exposure to AEDs has recently been questioned by Gaily and Granström from Finland, however.⁵¹ In a controlled, prospective study of 121 children born to mothers with epilepsy and in a control group of 105 children who had been examined for 80 minor anomalies in a blinded fashion, some anomalies regarded as typical for the fetal hydantoin syndrome were, in fact, associated with maternal epilepsy.^{51,52}

The clearest evidence for inheritance was obtained for epicanthus, which was strongly associated with epicanthus in the mother. Of the features investigated, only hypertelorism and digital hypoplasia were associated with exposure to phenytoin. Results suggested that in addition to the teratogenic effects of phenytoin, a genetic influence from the mother made a significant contribution to the development of hypoplasia.^{51,52}

Early results from Berlin⁵³ and Seattle³⁸ are in agreement with the Gaily and Granström experience. Neither study, however, has reached completion, and the cohort is small in the Seattle study. In both studies, epicanthus and anomalies of the root of the nose have not been correlated with phenytoin treatment.

The Berlin group observed that hypoplasia of nails and distal phalanges was associated predominantly with phenytoin monotherapy, but also in some cases with carbamazepine, phenobarbital, primidone, and valproate monotherapy.⁵³ Gaily and Granström^{51,52,54,55} also observed that distal digital hypoplasia was not associated with major malformations or cognitive impairment, as Hanson et al^{47,48} had presumed.

Yerby and collaborators from Seattle have shown that in 64 cases and 46 controls, infants of mothers with epilepsy have a higher mean number of minor anomalies (5.05) per child than do control children.³⁸ No differences have been found in the mean number of minor anomalies in children exposed to AED monotherapy as opposed to AED

polytherapy. With monotherapy, no dose-response effect of AED on the number of minor anomalies or any excess of a specific dysmorphic feature has been associated with a particular AED. With the exception of a prominent occiput, no particular minor anomaly occurred more commonly in infants of mothers with epilepsy treated with an AED than in control children.

Certainly, when noted at birth, these features can be quite distressing for the families. The findings of recent studies by Koch et al²⁴ might console such families. Nail and phalangeal hypoplasia and craniofacial hypoplasia, regarded as typical of AED exposure, tended to grow out in infancy, and the difference, except for hypertelorism,²⁴ was no longer statistically significant by 4 years of age.

On the basis of this recent information, Janz considers AED-specific fetal dysmorphic syndromes to be a scientific myth. Others, however, still ascribe a significant teratogenic role for AEDs in the production of some dysmorphisms.⁵⁶⁻⁵⁹ Furthermore, one cannot discount teratogenic effects of AEDs, such as phenytoin, carbamazepine, and valproate, in experimental animals.^{56,57} All now agree that the contribution of AEDs to the production of AED-specific fetal dysmorphic syndromes should be studied in a larger cohort of AED-exposed pregnant women with epilepsy. The role of genetic predisposing factors and specific AED monotherapies in the production of dysmorphic minor anomalies can then be investigated more specifically.

Does in utero exposure to AEDs induce prenatal and postnatal growth retardation? Infants exposed in utero to AEDs have been reported to be born small for gestational age, with a small head and subsequent impaired growth rate and cognitive development.^{16,18,23,26,47,53,60} Some investigators have found that AED-exposed infants had minor differences in length and weight at birth as compared with controls. Ascribing all these observations to AED exposure is difficult, however, because many factors are involved in prenatal and postnatal growth. Some differences could, in part, be explained by the slight difference in gestational age and parental height⁶¹ or by parity.

In the Finnish study, growth retardation in the first months was transient and related, in part, to suboptimal feeding associated with sedative drug effects. Slow weight gain was most prominent in the barbiturate-exposed subgroup, less prominent in phenytoin-exposed children, and almost nonexistent in the carbamazepine-monotherapy subgroup.⁵⁵

The Finnish investigators showed that head circumference at birth and at 18 months of age was significantly reduced in infants exposed to carbamazepine monotherapy or to drug combinations including barbiturates. The incidence of microcephaly in these infants, however, was not higher than in the general population at 5.5 years of age.⁶² Relatively small head circumferences in some AED-exposed children of mothers with epilepsy

were ascribed, in part, to genetic causes, since paternal head circumference was also below average in the same subgroups of children having the lowest mean values. Gaily et al⁶² do state that "a mild drug effect in the barbiturate- and carbamazepine-exposed children cannot be excluded."

In the San Diego cohort of Jones et al,⁵⁰ microcephaly (11%) was observed together with postnatal growth deficiency (6%) and developmental delay (20%) in infants of 50 mothers with epilepsy receiving carbamazepine monotherapy. Isolated microcephaly also was observed among 229 offsprings of AED-treated mothers with epilepsy in the Marseilles study, eg, lower than 3 standard deviations (SD) below the mean in 6.5% of 15 infants, and between 2 and 3 SD lower in 8.7% (20 other infants).³⁷ Unfortunately, in both these studies, data on matched controls and parents are lacking.

Does in utero exposure to an AED impair postnatal intellectual development? Prospective mothers often ask whether in utero exposure to AEDs retards children's postnatal intellectual and cognitive development. In the 1970s and 1980s, such effects were considered likely because of a belief extant in the pediatric neurology community that postnatal exposure to these same AEDs during the first years of life impairs development of motor, intellectual, and cognitive functions. In fact, most previous studies showed a very small risk for low general intelligence among children treated with AEDs early in life.

In utero exposure to one AED might be a different matter. Not all parties agree on the potential risks of prenatal exposure for postnatal motor development and cognition. Studies are now in progress; the only adequate reports to date are by Gaily and Granström.^{51,54} These investigators studied motor and specific cognitive abilities of 104 children of mothers with epilepsy and 105 controls at the age of 5 ½ years. The risk of mental deficiency was only slightly increased (1.4% greater than in controls). A lower IQ score also was associated with a high number of minor anomalies. Most children of mothers with epilepsy developed normally with regard to motor functions but had some type of specific cognitive dysfunction. The increased risk was not associated with exposure to AEDs but with seizures during pregnancy, specifically with partial seizures in mothers, and with low paternal education.

The authors discussed three possible mechanisms for specific cognitive dysfunction in children of mothers with epilepsy: subtle brain damage associated with fetal asphyxia during generalized convulsions of the mother (but some children were exposed to nonconvulsive maternal seizures), genetically transmitted brain abnormalities (but children of mothers with primarily generalized epilepsy were less affected), and a psychosocial disadvantage limiting partner choice.^{51,54}

Because frequent seizures might limit the women's choice of a partner, the genetic constitution of the offspring associated with decreased cog-

nitive function also might be inherited from the father. Uncontrolled epilepsy in the mother also might well impair the parent-child relationship and thus have an impact on the mental and emotional development of the child. Because seizures during pregnancy, epilepsy itself, and socioeconomic or psychosocial factors all affect the cognitive development of children of mothers with epilepsy, it is difficult to blame a single AED.

Future studies on AED teratogenesis. Clearly, more prospective, controlled studies are needed to establish the dire, but rare, effects of AED exposure in utero on prenatal and postnatal growth and postnatal intellectual development. The true prevalence of major malformations and dysmorphism in a large cohort population (at least 1,600 pregnancies) needs to be determined. Only a large cohort study will permit any decision about which AED is a more dangerous teratogen and whether frequent grand mal tonic-clonic convulsions can do irreparable and permanent harm to the fetus and lead to miscarriages and stillbirths. Furthermore, such a study should use an established, comprehensive uniform protocol, such as that used by the ILAE Commission on Epilepsy, Pregnancy, and the Child.

Another benefit of a large cohort study would be the inclusion of an adequate number of families to permit a decision about whether a genetic predisposition to epilepsy and birth defects, such as facial clefts and neural-tube defects, exists. In a population-based, historical cohort study by Hecht et al,⁶³ the incidence of epilepsy was not increased among relatives of probands with orofacial clefts. Kelly et al⁶⁴ and Dronamraju⁶⁵, on the other hand, observed an increased prevalence of epilepsy among relatives of patients with facial cleft. Friis et al^{66,67} also noted that the prevalence of facial clefts was twice as high among 3,203 unselected patients with epilepsy. The prevalence of cleft lip and palate was increased only when the mother had clinically manifested epilepsy. It was not increased in children of fathers with epilepsy.

Neural-tube defects also are influenced by genetic factors. Children of patients with generalized epilepsies have spina bifida occulta more often than expected by chance.^{68,69} Robert and Guibaud,²⁷ in their study of valproate-treated mothers, noted that three of nine infants with neural-tube defects had a relative with spina bifida. More recently, Lindhout et al³² found equal numbers of positive maternal and paternal family histories in 34 infants with neural-tube defects whose mothers had been receiving AEDs—mostly valproate or carbamazepine. The family history of the pregnant mother who is exposed to AEDs, as well as the family history of her husband, should therefore be probed for these major birth defects.

Should AEDs be withdrawn from women planning pregnancy? Despite the foregoing

Table 3. Guidelines: antiepileptic drugs (AEDs) during pregnancy

1. Use first-choice drug for seizure type and epilepsy syndrome.
2. Use epileptic AED as monotherapy at lowest dose and plasma level that protects against tonic-clonic seizures.
3. Avoid valproate and carbamazepine when there is a family history of neural-tube defects.
4. Avoid polytherapy, especially combination of valproate, carbamazepine, and phenobarbital.
5. Monitor plasma AED levels regularly and, if possible, free or unbound plasma AED levels.
6. Continue folate daily supplement and ensure normal plasma and red cell folate levels during the period of organogenesis in the first trimester.
7. In cases of valproate treatment, avoid high plasma levels of valproate. Divide doses over 3 to 4 administrations per day.
8. In cases of valproate or carbamazepine treatment, offer amniocentesis for α -fetoprotein at 16 weeks and real-time ultrasonography at 18 to 19 weeks, looking for neural-tube defects. Ultrasonography at 22 to 24 weeks can detect oral clefts and heart anomalies.

observations, the identified risks of AEDs during pregnancy do not present an insurmountable barrier to their use in women whose seizures continue to recur before and during pregnancy (table 3). Neither, however, can the rare risks (especially the major malformations) associated with AED use during pregnancy be judged trivial. Given the inarguable nature of the evidence so far adduced in support of the rare teratogenic effects of the four major AEDs, their withdrawal in patients planning pregnancy who have been free of seizures for at least 2 years may be considered. Slow withdrawal of AEDs over 3 months can be done safely with close outpatient and inpatient clinical and electroencephalographic monitoring in 25 to 30% of women planning pregnancy.

In 2,165 pregnancies of women with epilepsy reported by Schmidt et al,⁷⁰ 53.2% had a decrease, 24% had an increase, and 22.7% had no change in seizure frequency during pregnancy. Koch et al²⁴ noted grand mal seizures during pregnancy in 47 of 116 women with epilepsy. If patients experience exacerbations of seizures during pregnancy, 50% will do so at 8 to 16 weeks and another 35% will at 16 to 24 weeks of pregnancy. One should guard carefully against repeated and recurring tonic-clonic convulsions. Status epilepticus, however, is not more common in pregnant women with epilepsy than in nonpregnant women with epilepsy. In fact, it is a rare complication of pregnancy. Bardy did not find any case of status epilepticus in his prospective study of 154 pregnancies of epileptic women,⁷¹ and it was rarely or never observed in most of the modern prospective series studying AED-associated teratogenesis.^{31,34,35,37}

In pregnant women, the high percentage of birth defects associated with polypharmacy pre-

cludes the use of AEDs in combination.^{24,29,42,53} Crossover from polypharmacy to monotherapy should therefore be attempted before conception and started with the gradual introduction of a first-choice drug. When therapeutic plasma levels of that drug are reached, the doses of other drugs can gradually be reduced. If the first-choice drug is one of the drugs already being used in combination, the dose is maintained or increased as the others are gradually withdrawn. Commonly, as drugs are withdrawn, plasma levels of the first-choice drug increase. Nonessential drugs and those with interactions and adverse side effects are withdrawn first. Withdrawal usually occurs over a 1- to 3-month period, with monitoring of plasma drug levels. In 36% of cases of polypharmacy withdrawal, successful control can be achieved with monotherapy.

Unfortunately, no study is available on AED withdrawal in women planning pregnancy and during pregnancy. Nevertheless, results of AED withdrawal in the epilepsy population at large who have achieved control can guide us in the withdrawal of AEDs in women planning pregnancy. Relapse of seizures occurred after withdrawal of AEDs in 17 to 63% of patients whose seizures had been completely suppressed for 2 to 5 years with AED treatment.^{72,73} Risks for relapse increase when the history includes clonic-tonic-clonic grand mal convulsions, myoclonias, or awakening seizures (myoclonias, tonic-clonic grand mal); prolonged seizures or convulsive status breaking through AED treatment; or when seizure control has been achieved with a combination of two or three drugs.

Clearly, we should be hesitant, if not cautious, in withdrawing AED treatment from women planning pregnancy if their history includes the above risks for relapse. In the Medical Research Council (MRC) Antiepileptic Drug Withdrawal Study,⁷² which used a randomized, parallel-group design, 12% of patients relapsed during the first 6 months of drug withdrawal, 32% during the first year, and 41% during the first 2 years. Since we generally withdraw AEDs in the 2 to 4 months immediately preceding attempts for conception, a small percentage (approximately 12%) can be expected to relapse within these 2 to 4 months and during the first trimester. If the MRC study is used as a model of AED withdrawal, at least 28% would relapse sometime during pregnancy.⁷² The MRC study also showed that there are no significant differences in the risk of relapse for patients on monotherapy with carbamazepine, phenobarbital, phenytoin, or valproate.⁷²

After monotherapy is established, the lowest plasma AED level below which seizures occur should be determined. During a conference with the patient and her partner, the medical and social problems surrounding breakthrough seizures should be discussed, and a joint decision made by the patient and her physician about whether to continue dose reduction.

Should folic acid be given as a supplement before conception? Whether folate supplements given before and early in pregnancy prevent neural-tube defects in the infants of AED-treated women with epilepsy has not yet been conclusively determined. Reports from experiments in animals and studies of women without epilepsy, however, suggest that folate supplementation before and during pregnancy might be prudent.

Wegner and Nau⁷⁴ found that teratogenic doses of valproate that produced exencephaly in a murine model also reduced concentrations of formylated tetrahydrofolates and increased levels of tetrahydrofolate in embryonic tissue. Presumably, valproate inhibited glutamate formyltransferase. Folinic acid, administered before and after a teratogenic dose of valproate, significantly reduced the number of newborn animals with valproate-induced exencephaly.⁷⁴ In 1984, Billings⁷⁵ observed that phenytoin also decreases levels of 5,10-methylenetetrahydrofolate in treated dams, suggesting that altered concentrations of specific folate forms could have adverse effects on embryonic development.

Earlier human studies relating folate levels in plasma and red cells with birth defects in the offspring of women with epilepsy perhaps have produced conflicting data, as Dansky et al³⁵ suggest, because of variability in methods and timing of the folate determinations. Even earlier, large studies on periconceptional supplementation with multivitamins and folic acid in women without epilepsy to prevent neural-tube defects produced opposite conclusions.^{76,77} Recent results from the MRC vitamin study⁷⁸ (women with epilepsy were excluded from this study), have firmly established, however, that folic acid supplementation starting before pregnancy can have a 72% protective effect in preventing neural-tube defects (anencephaly, spina bifida, and encephalocele) in women at high risk for having a fetus with a neural-tube defect.

In the 1,817 women participating in this international, multicenter study,⁷⁸ a previous pregnancy had resulted in a child with neural-tube defects. The women were allocated at random to groups that received folic acid, other vitamins, both, or neither. Other vitamins showed no significant protective effect, and folic acid supplementation had no demonstrable harmful effect. No similar study has been performed in women with epilepsy at high risk for having a fetus with a neural-tube defect. Ogawa et al⁷⁹ did, however, relate low serum folate levels in the first trimester of pregnancy to the occurrence of malformations in infants born to women with epilepsy. Thus, it might be safer at the present time to ensure that the diets of all women who might bear children contain adequate amounts of folic acid, that all women with epilepsy who are under treatment with AEDs receive folic acid daily, and that pregnant women with epilepsy receiving AEDs be determined to have normal folic acid concentrations in serum and red cells.

In the Montreal prospective study of 116 pregnancies of women with epilepsy, combination therapy with phenytoin, phenobarbital, or primidone; high plasma levels of phenytoin and phenobarbital; and serum folic acid levels of <4 mg/mL before pregnancy and early in pregnancy were associated with spontaneous abortions and developmental anomalies (ventricular septal defect, hypertrophic cardiomyopathy with endocardial fibroelastosis and conduction defect, cleft lip and palate, hydrocephalus due to Dandy-Walker syndrome and hypospadias).³⁵

Offering prenatal diagnosis. In many women with epilepsy, tonic-clonic and frequent complex partial seizures pose a danger for the patient. For these women, AED treatment cannot be avoided. In such circumstances, the possible teratogenic risks of the specific AED should be weighed against the type and severity of the patient's epilepsy.

The patient's attitude toward amniocentesis and possible termination of pregnancy must be considered and openly discussed as early as possible, in the event that a severely malformed fetus is detected in subsequent tests and examinations. For some patients, particularly those with a family history of neural-tube defects, the risks of neural-tube defects in offspring associated with maternal valproate therapy (1 or 2%)³⁰⁻³² or carbamazepine therapy (0.9 to 1%)³³ justify consideration of the replacement of these drugs with another AED, such as clonazepam. A fetal benzodiazepine syndrome has been described,⁸⁰ but incomplete information exists as to whether clonazepam, when used as monotherapy, is teratogenic.

Nakane et al^{15,17} suggest that polytherapy with regimens including diazepam is associated with major congenital defects. In contrast, Starreveld-Zimmerman et al⁸⁰ did not find malformations after in utero exposure to diazepam or benzodiazepines, and Rosenberg et al⁸¹ noted no relation of oral clefts to diazepam use during pregnancy.

If seizures respond only to valproate or carbamazepine treatment and if the patient accepts treatment with one of these drugs, the dosage of either drug should be reduced to the minimum that protects against convulsions before conception. Serum and red cell folate levels should be monitored and folic acid supplements given to ensure adequate blood folate levels. At weeks 5 to 6 and week 10 of pregnancy, serum levels of AEDs should be checked to evaluate the environment for fetal organogenesis.²

Prenatal diagnosis with amniotic fluid analysis of α -fetoprotein (AFP) at 16 weeks and ultrasonography at 18 to 19 weeks should be offered.^{2,31,92} Some disagreement remains about whether amniocentesis for AFP quantitation should be routinely offered and whether it should preclude serum AFP determinations.⁸³ Some centers prefer amniotic fluid determinations to serum measurements, because the latter can miss 20 to 25% of neural-tube defects.³¹

Others argue that the risk of neural-tube defects is less than 1% when both the serum AFP value and the results of an ultrasound scan are normal. This should be weighed against the 1% risk for miscarriage associated with amniocentesis. This approach argues further that high-resolution ultrasonography in the hands of an experienced examiner can detect more than 94% of neural-tube defects and that amniocentesis should be reserved for patients with elevated serum AFP levels or for those for whom an ultrasound scan fails to exclude a neural-tube defect with any reliability.^{2,83}

With other AEDs, such as phenytoin and phenobarbital, the risk of such malformations as heart defects and facial clefts also warrants the offering of prenatal diagnosis by ultrasonography at 20 to 24 weeks. According to Hiilesmaa,² a four-chamber view at 18 to 19 weeks can exclude many heart malformations incompatible with life, and an optimal diagnosis of fetal cardiac defects requires the use of color Doppler imaging. Bilateral radial aplasia, a rare but specific effect of valproate therapy, might also be diagnosed by ultrasonography.

With respect to phenytoin, preliminary evidence suggests that it is possible to identify fetuses at increased risk for phenytoin-induced congenital malformations, including impaired intellectual development, by measuring epoxide hydrolase activity in fetal amniocytes.⁵⁹ In this study in 19 pregnancies exposed to phenytoin monotherapy, four infants were identified with low amniocyte epoxide hydrolase activities. After delivery, all four infants had the stigma of AED-induced dysmorphisms. Two of these four infants had significantly delayed motor development. Such a procedure requires cell culture of amniocytes obtained during amniocentesis, and further studies are required to assess the practicality of these findings for routine patient care.

Use of one AED during pregnancy: lowest effective dose. During follow-up of the pregnant woman with epilepsy, the principles of sound AED therapy must be applied (table 3). The lowest effective dose is used, and almost always a single AED is prescribed. For valproate, the use of a single daily dose is not advisable because the adverse effects are believed to be the result of unpredictably high peak levels.⁸⁴ Total serum AED levels, and if possible, free AED fractions, should be measured at regular intervals throughout pregnancy.⁸⁵ Multiple drug doses are spread out over the day, in three or four doses.

Mean concentrations of the four frontline AEDs decline as pregnancy progresses, but free fractions decline significantly only for phenobarbital.⁸⁶⁻⁸⁷ A decrease in serum AED levels does not in itself justify an increase in dosage. The overall clinical state should be assessed. Increased hepatic and renal clearance rates, reduced albumin levels, plasma protein binding of increased levels of unbound drug, and increased plasma volume by the third

trimester all can contribute to lowered plasma AED concentrations.⁸⁸ Plasma levels of ethosuximide usually remain fairly constant during pregnancy.

Unfortunately, some women remain uninformed about the risks of AED use during pregnancy. Often they first realize they are pregnant late in the first trimester, when major organ systems already have formed and potential congenital malformations already might have developed. Not infrequently, these women are receiving polytherapy, and the clinician is faced with the dilemma of risking the occurrence of seizures in the patient while she is shifted to monotherapy or exposing the fetus to multiple AEDs. Such a clinical setting is far from ideal, and clinical judgments should be individualized to fit the specific circumstances. In general, however, monotherapy should be considered as soon as pregnancy is disclosed.

Labor, delivery, and birth. Most women with epilepsy have a normal vaginal delivery.^{2,40,89} Risks for the mother and infant are present in the rare women whose convulsions or complex partial seizures continue to be intractable to treatment during the third trimester and often occur as weekly attacks, as seizures in clusters, or as status epilepticus during severe stress. The threat of fetal asphyxia caused by repeated tonic-clonic seizures or convulsive status epilepticus during labor might justify an elective cesarean section.^{10,11,20,89} Prompt cesarean section should be performed when repeated tonic-clonic convulsions cannot be controlled during labor or when the mother is unable to cooperate during labor because of impaired awareness during repeated absences or psychomotor seizures.²

A tonic-clonic seizure occurs during labor in 1 to 2% of women with epilepsy, and 24 hours after delivery in another 1 to 2%. Maintenance of plasma AED levels known to protect against seizures during the third trimester is a preventive measure against the occurrence of seizures during labor. Taking AEDs during labor to ensure adequate plasma levels is also important, and the patient must be cautioned against missing doses as labor continues.^{10,11,88}

Convulsive seizures during labor and delivery should be treated promptly and are best managed with intravenous benzodiazepines. Intravenous lorazepam is suggested as a drug of choice to stop repeated seizures during labor.⁸⁸ Disagreement exists as to whether phenytoin should be used to stop repeated convulsions during labor, because phenytoin inhibits myometrial contraction and might prolong labor.⁹⁰

A majority consider it prudent to administer vitamin K₁ (20 mg/d) prophylactically to the AED-treated mother during the last month of pregnancy, as a means of protecting the infant against severe postnatal bleeding caused by a deficiency of vitamin K₁-dependent clotting factors II, VII, IX, and

X.^{88,91,92} A minority disagree.² All agree, however, that the newborn should receive 1 mg of vitamin K intramuscularly at birth as a prophylactic measure. This hemorrhagic disorder is not rare and can occur in infants of mothers with epilepsy treated with phenobarbital, primidone, phenytoin, carbamazepine, diazepam, or ethosuximide, and even independent of AEDs.³

Mortality from this postnatal bleeding disorder is high (>30%), because internal bleeding in abdominal and pleural cavities occurs within the first 24 hours and is not noticed until the infant is in shock. Mountain et al⁹³ found this coagulation defect in 8 of 16 neonates born to 16 unselected women with epilepsy, and Vert et al⁹⁰ in 7 of 115 infants of mothers with epilepsy. Cord blood will show diminished levels of clotting factors and prolonged prothrombin and partial thromboplastin times. If any two of the coagulation factors II, VII, IX, and X fall below 25% of normal values, intravenous administration of fresh-frozen plasma will be necessary.⁹⁴

AEDs during puerperium. If AED dosages are increased during pregnancy, they must be returned to prepregnancy levels during the first weeks of puerperium, to avoid toxicity. A rebound increase in AED levels can occur, such as with phenytoin, in the postpartum period. Drug levels must be checked periodically for at least the first 2 months after delivery.

All of the four frontline AEDs (phenytoin, carbamazepine, phenobarbital, and valproate), as well as ethosuximide, primidone, and benzodiazepines, are measurable in breast milk. Reported concentrations of AEDs in breast milk range from levels of 10 to 60% or 40 to 80% of maternal serum levels.⁹⁵⁻¹⁰¹ In general, taking AEDs for epilepsy does not constitute a contraindication for breast feeding. The exceptions are sedative AEDs, such as phenobarbital, primidone, or benzodiazepines.^{100,101} A sedative AED can cause an infant to be irritable, fail to thrive, and fall asleep shortly after beginning to nurse.

After delivery, phenobarbital, primidone, and benzodiazepines will remain in neonatal plasma for several days, causing sedative effects and possibly a neonatal withdrawal syndrome. Concentrations of phenobarbital in breast milk are 36 to 40% of the concentrations in maternal serum. The plasma half-life of phenobarbital in the postnatal period (40 to 300 hours) is considerably longer than in adults. It is even longer in premature infants. The free fraction of phenobarbital increases to more than 90% of the total serum concentration in some infants and increases sedative effects.¹⁰⁰

Concentrations of diazepam and N-desmethyldiazepam in breast milk are 4 to 10 times lower than those in plasma. Concentrations of lorazepam in breast milk are approximately 20% of the total maternal serum concentrations.¹⁰² The concentration of valproate in breast milk is 5 to 10% of the

maternal serum concentration.^{97,99} Concentrations of ethosuximide in breast milk are approximately 90% of the steady-state plasma levels in maternal plasma.^{95,98}

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